DECLARATION OF
DR. MANFRED BOHN

PATE
Attorney Docket No. 2481.1580-00(

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	
Manfred BOHN et al.	
Serial No.: 09/135,657	Group Art Unit: 1615
Filed: August 18, 1998	Examiner: A. Berman
For: Antipsoriatic Nail Polish	

DECLARATION OF MANFRED BOHN

I, Manfred Bohn, of Aventis Pharma Deutschland GmbH, Industriepark Höchst, Building D 528, 65926 Frankfurt am Main, Germany do declare that:

1. I am Director and Head of Preclinical Development Dermatology at Aventis Pharma Deutschland GmbH. My work includes developing pharmaceuticals including those directed to diseases and conditions of the nail. I have been working as a pharmacist in pharmaceutical development for 32 years. I am a named inventor on the instant application, U.S. Serial No. 09/135,657.

2. I am also a named inventor on U.S. Patent No. 5,264,206 ("the Bohn patent"), a reference relied upon by the Examiner as prior art in the pending case. This patent is directed to pharmaceutical nail compositions for treating onychomycosis - an infectious disease -, a completely different disease condition than psoriasis, the disease condition of the instant application – which is caused mainly by autoimmune

mechanisms. The active ingredient in the antimycotic compositions of th Bohn pa are a different class of chemical compounds than those of the instant application.

3. The invention in the instant application is directed to a composition comprisin glucocorticoid, a water-insoluble film-forming agent, and a physiologically tolerable solvent. This invention is able to deliver a pharmacologically active amount of anti-psoriatic agent to the affected nail without the disadvantages found in previous anti-psoriatic nail polishes as discussed in the instant application at pages 1-4. These disadvantages include long-term treatment leading to intoxication, painful injections, temporary intervention by surgical removal, psychological distress due to multiple nail treatments , and lack of bioavailability.

4. The Examiner has cited U.S. Patent No. 4,250,164 to Bernstein ("the Bernstein patent") in combination with the Bohn patent discussed above. I understand that the Examiner seeks to combine the Bernstein patent teachings on the use of glucocorticoids with the water-insoluble film formers taught by the Bohn patent to produce a composition of the instant invention, in order to question the novelty and inventive step of the instant invention.

5. I have performed a series of experiments to show that the teachings of the Bernstein patent cannot be combined with the Bohn patent - as the Examiner propos s – due to a physical incompatibility. In brief, these experiments prove that one does not obtain a stable mixture upon combining the glucocorticoids of the Bernstein patent with

a typical water-insoluble film former, such as a commercially available Revlon® cle nail polish.

6. Exhibit A shows a photograph of 4 bottles labeled 1 through 4. Bottles 1 and each contain a 0.1% valisone lotion I prepared as described in the Bernstein patent. (col. 1, lines 50-61). Bottles 3 and 4 each contain a commercially available Revlon® clear nail polish.

7. Exhibits B through E show photographs of mixtures of Revlon® clear nail polish and 0.1% valisone lotion taken at 45 seconds, 4 minutes, 7 minutes and 15 minutes after pouring carefully - without any mixing - valisone lotion on top of Revlon clear nail polish (3) or vice verse (2). As Exhibit B shows, after only 45 seconds, a precipitate forms due to the unstable nature of combining the aqueous-based 0.1% valison lotion with the water-insoluble nail polish. The situation worsens during the course of the experiment. 2 minutes and 1.5 hours, respectively, after mixing both bottles 2 and 3 contain significant precipitates (Exhibits F+G). 20 hours after mixing the precipitates have formed a clot (Exhibit H), which cannot be shaken up again (Exhibit I).

8. The invention of the instant application does not precipitate upon combining the glucocorticoid with the water-insoluble film former of the invention because, other than water found in the solvent used, the compositions taught are substantially wat r free. Because the instant invention does not precipitate and is therefore, stable, it can be used as a pharmaceutically effective anti-psoriatic medicament.

9. By comparison, the Bernstein patent teaches using glucocorticoid solutions containing water. Indeed, water is taught as a specific ingredient in the vehicle containing vallsone solution, (col. 1, lines 50-61). The Bohn patent is direct d primari. to non-aqueous compositions for delivering antimycotic compounds. For instanc , the 0.1% valisone solution taught by the Bernstein patent at col. 1, lines 50-61 contains or the order of about 50% water by weight. That these two references are not combinabl one need only consider the results in the attached Exhibits, clearly showing such mixtures to be inherently unstable and therefore not applicable.

10. In my opinion, before the instant invention was made, it was not believed possible to combine antipsoriatic compounds of the kind claimed in the instant application with water-insoluble film formers. Due to the different physicochemical nature of antimycotics in comparison to the mentioned antipsoriatics – which have a much higher molecular weight –, I do not believe that persons of ordinary skill would have read either of the cited patents as suggesting the combination of antipsoriatics with film formers. This is especially true taking into account that in transdermal drug delivery systems up to now only 7 compounds – which have to cross a much thiner keratin layer in comparison to nails – are successfully used. Furthermore, I do not believe that those of ordinary skill would have used an antimycotic composition and expect to produce an acceptable antipsoriatic nail polish.

I further declare that all statements made herein of my own knowledge ar tru and that all statements made on information and belief are believed to be true; and

further th se statements were made with the knowledge that willful false statements, and the like, so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of any patent issued thereon.

Manfred Bohn, PhD

Date: Nov. 21, 2000

EXHIBIT I

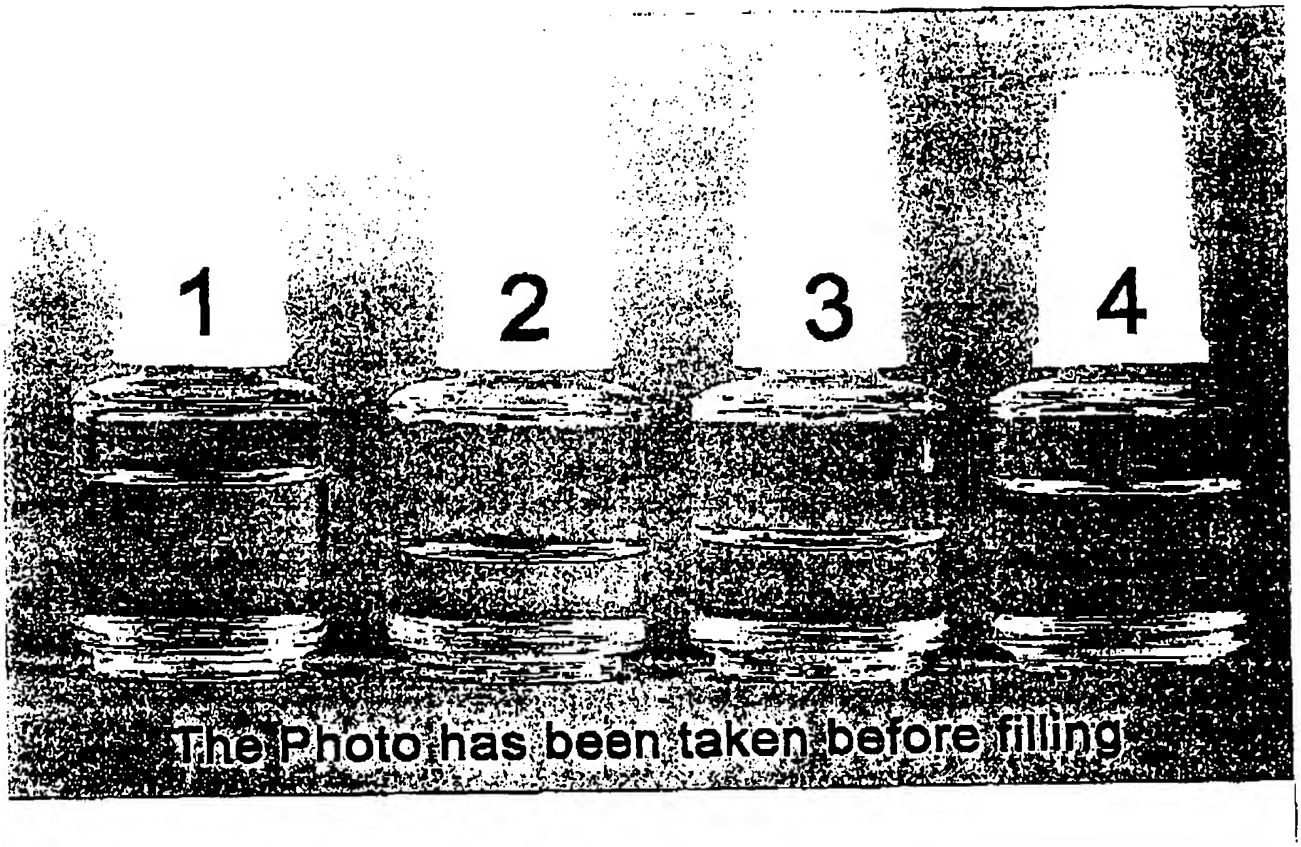
Exhibit Associated with
Dr. Manfred Bohn's Declaration

Customer No. 22,852
Attorney Dock t No. 2481.1580

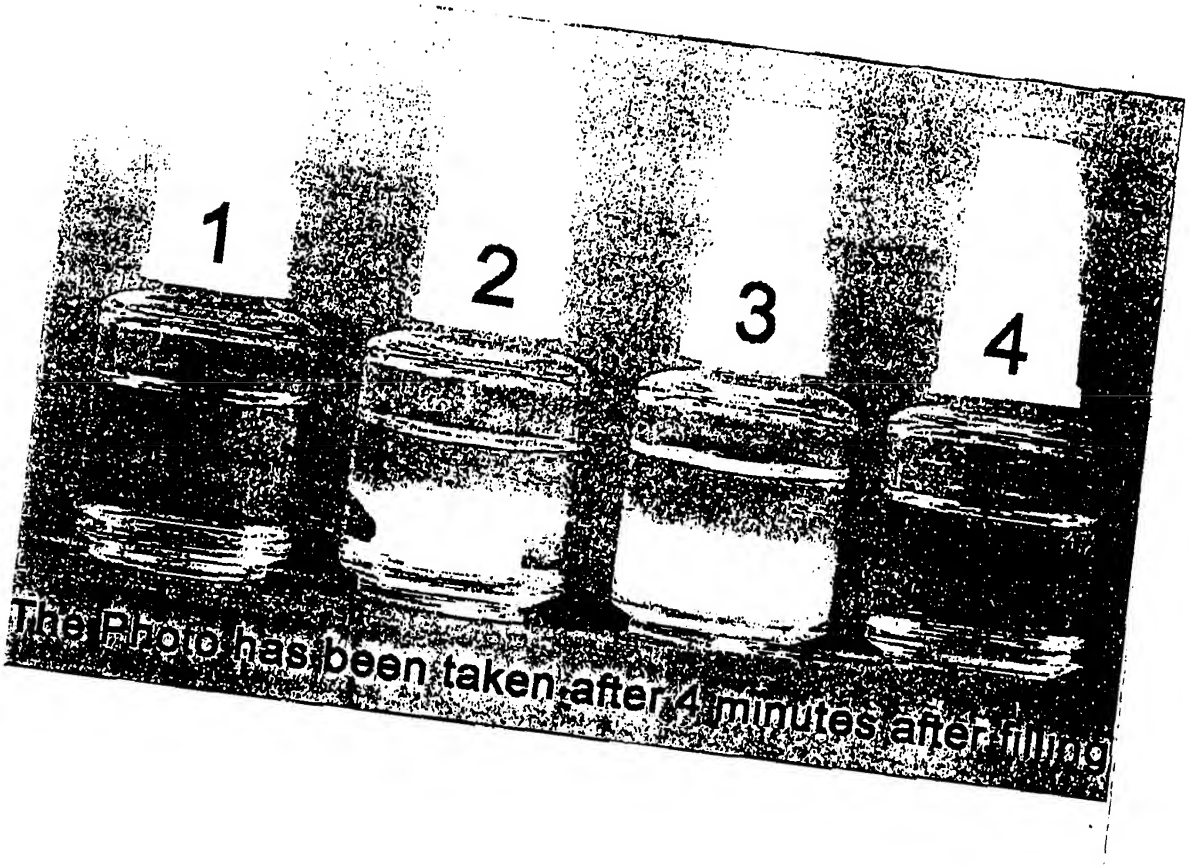
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

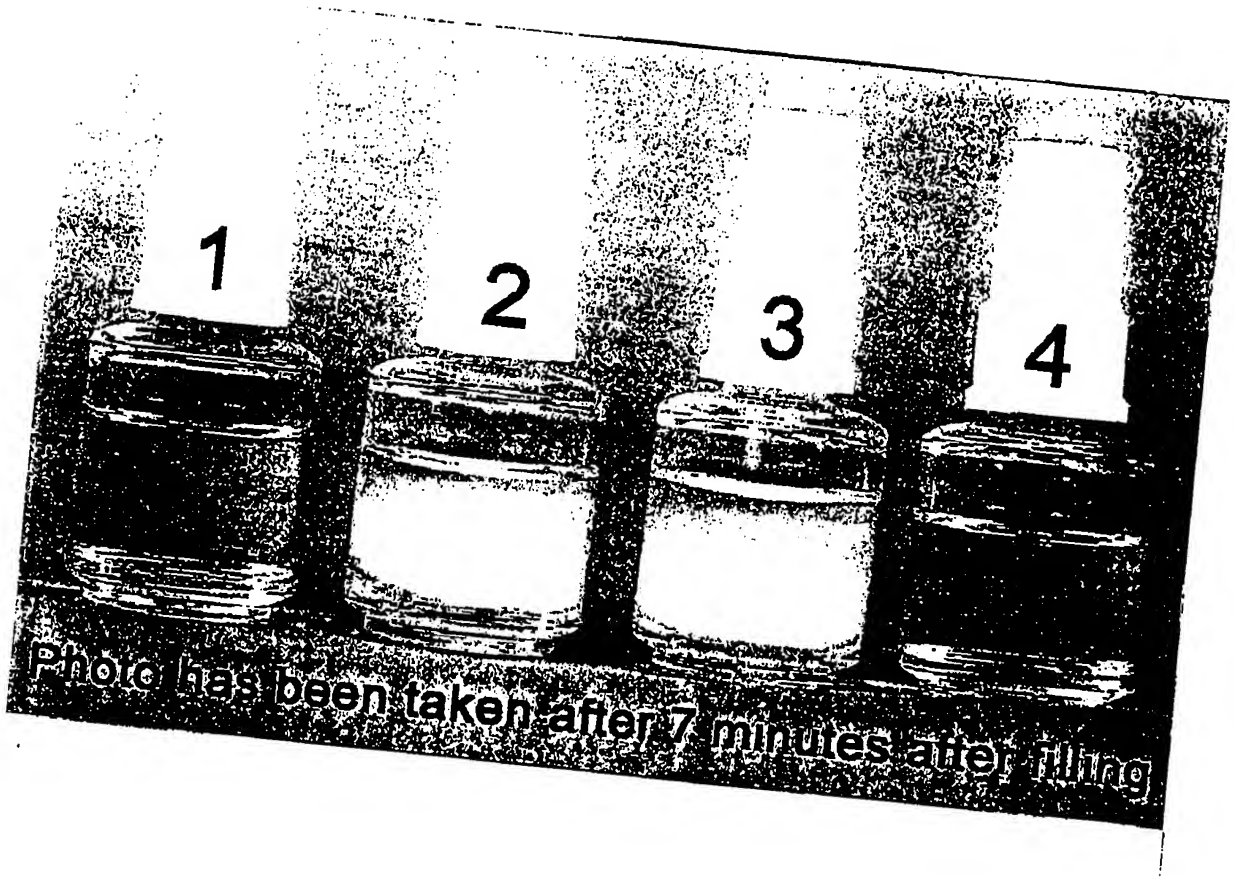
In re Application of	)	
	)	
Manfred BOHN et al.	)	
	)	
Serial No.: 09/135,657	)	Group Art Unit: Unknown
	)	
Filed: Herewith	)	Examiner: Unknown
	)	
For: Antipsoriatic Nail Polish	)	

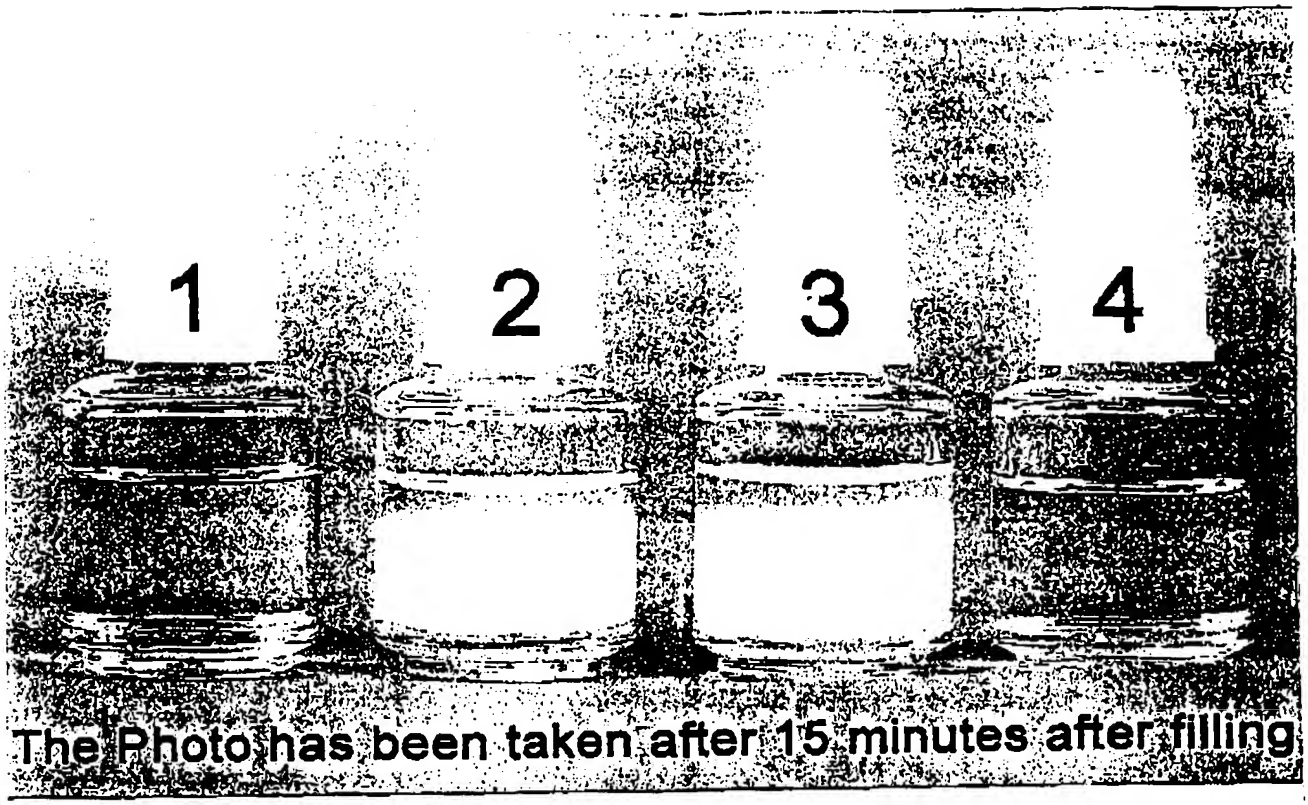
EXHIBITS TO DR. MANFRED BOHN'S DECLARATION


1
2
3
4
The Photo has been taken before filling

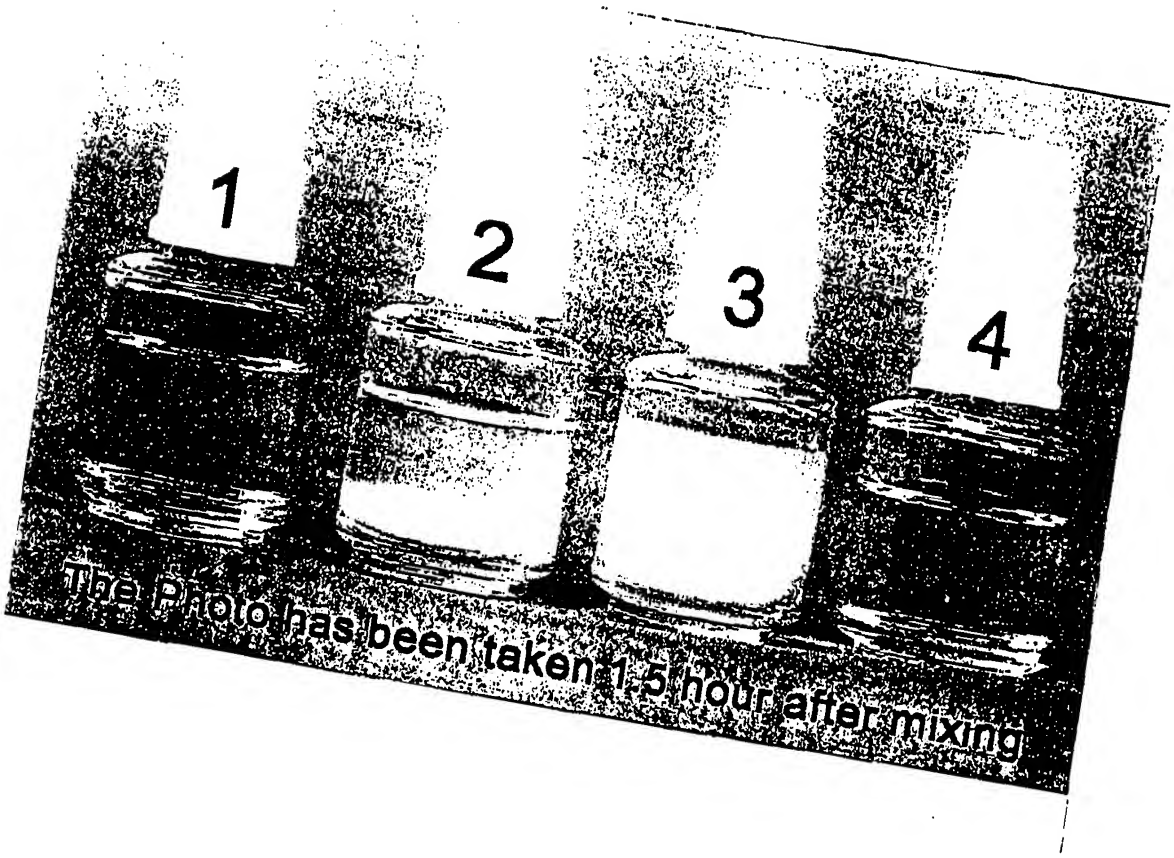

1
2
3
4
The Photo has been taken 45 seconds after filling

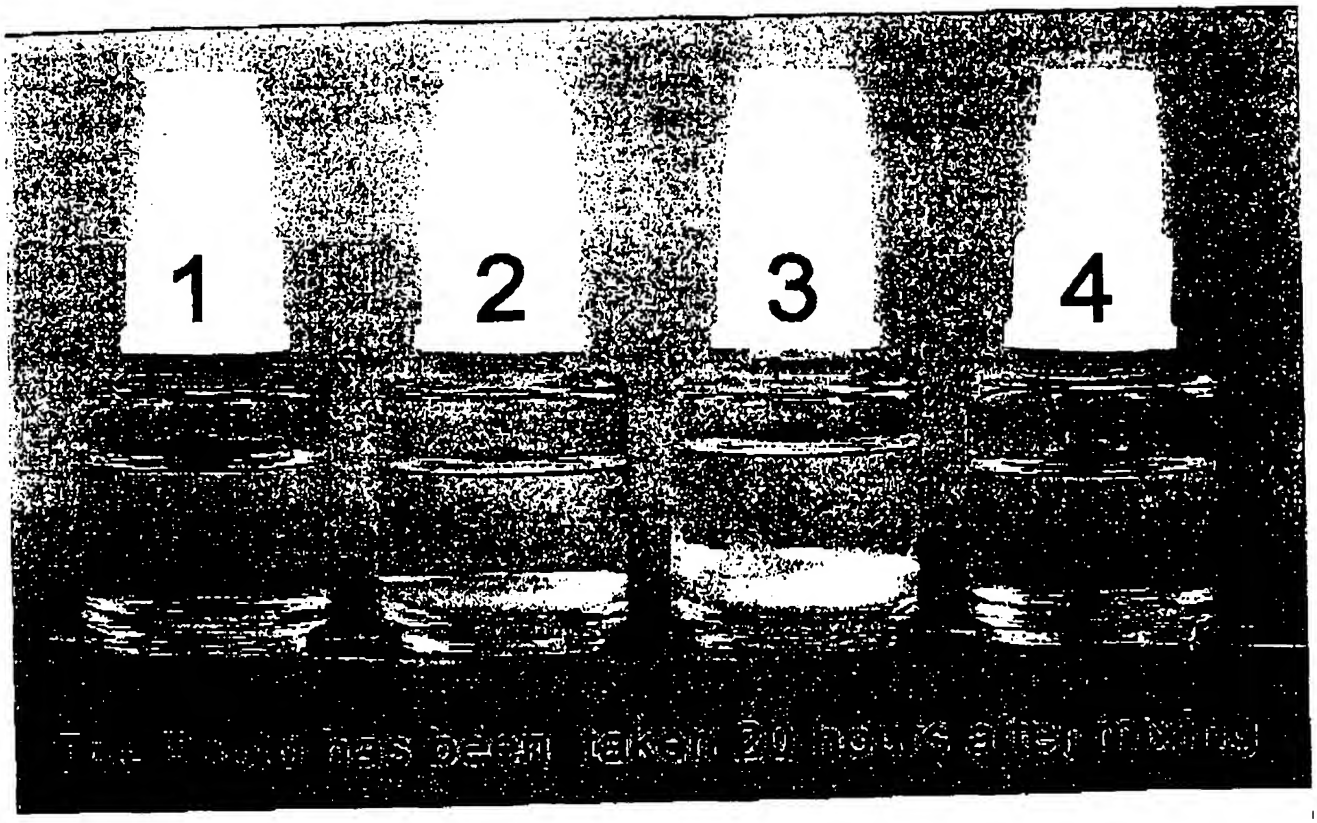

1
2
3
4
The Photo has been taken after 4 minutes after filling


1
2
3
4
Photo has been taken after 7 minutes after filling


1
2
3
4
The Photo has been taken after 15 minutes after filling


1
2
3
4
The Photo has been taken 2 minutes after mixing


1
2
3
4
The Photo has been taken 1.5 hour after mixing


1
2
3
4

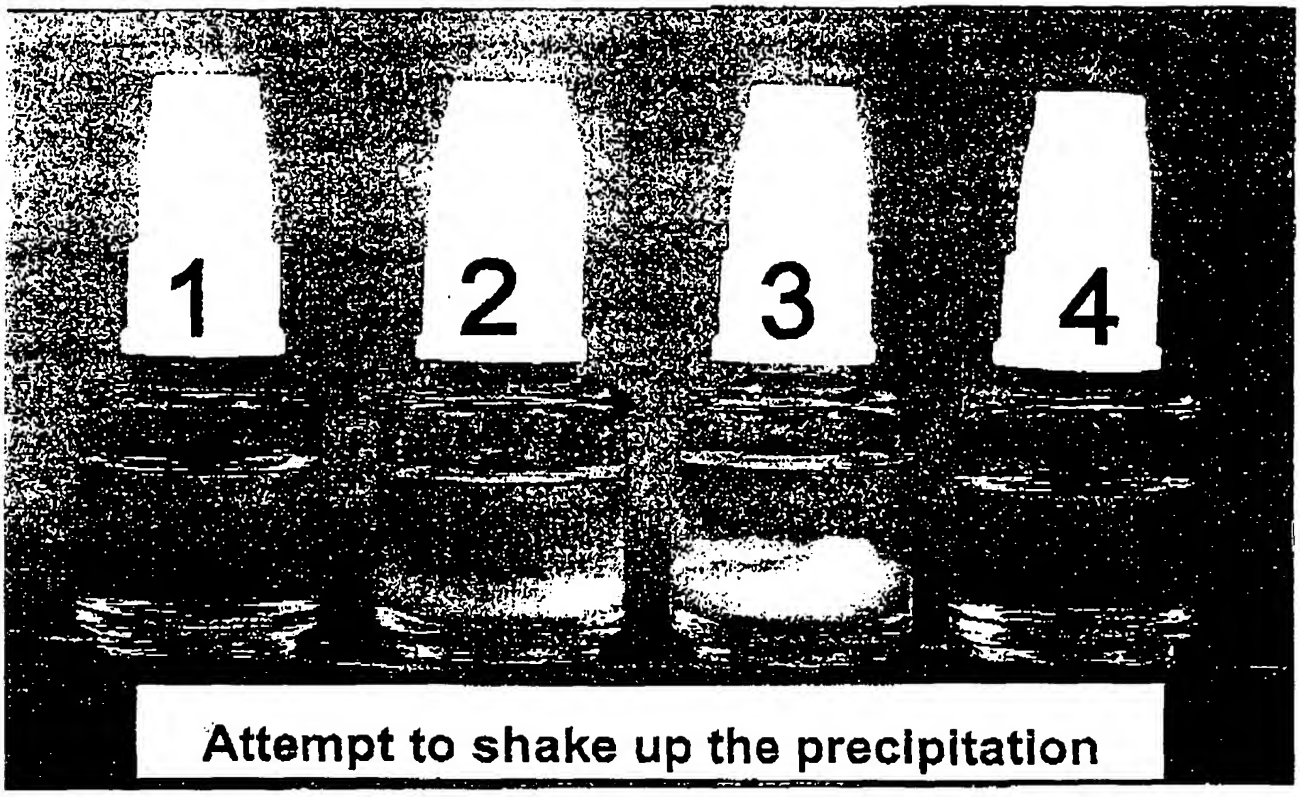

1
2
3
4
Attempt to shake up the precipitation

EXHIBIT II

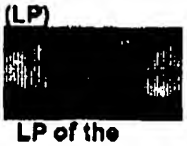
Potency Ranking of Some Commonly Used Topical Corticosteroids

EXHIBIT II

Vulva — Lichen Planus: Steroid Potencies

Potency Ranking of Some Commonly Used Topical Corticosteroids[1*]

Class	U.S. Brand Name	Generic name
I: Super High Potency	Temovate® Cream, 0.05%	clobetasol propionate
	Temovate® Ointment, 0.05%	clobetasol propionate
	Temovate® Gel, 0.05%	clobetasol propionate
	Temovate® E, 0.05%	clobetasol propionate
	Diprolene® Cream, 0.05%	betamethasone dipropionate
	Diprolene® Ointment, 0.05%	betamethasone dipropionate
	Diprolene® AF Cream, 0.05%	betamethasone dipropionate diflorasone diacetate
	Psorcon® Ointment, 0.05%	halobetasol propionate
	Ultravate® Cream, 0.05%	halobetasol
	Ultravate® Ointment, 0.05%	
	Temovate® Cream or Ointment is more potent than Diprolene® Cream or Ointment and Psorcon® Ointment	



II	Cyclocort® Cream, 0.1%	amcinonide
	Cyclocort® Ointment, 0.1%	amcinonid
	Cyclocort® Lotion, 0.1%	amcinonide
	Diprosone® Ointment, 0.05%	betamethasone dipropionate
	Florone® ointment 0.05%	diflorasone diacetate
	Halog® Cream®, 0.1%	halcinonide
	Halog® Ointment	halcinonide
	Lidex® Cream, 0.05%	fluocinonide
	Lidex® Ointment, 0.05%	fluocinonide
	Lidex-E® Cream, 0.05%	fluocinonide
	Maxiflor® Ointment, 0.05%	diflorasone diacetate
	Maxivate®, Ointment 0.05%	betamethasone dipropionate
	Topicort® Cream, 0.25%	desoximetasone
	Topicort® Gel, 0.05%	desoximetasone
	Topicort® Ointment, 0.25%	triamcinolone acetonide
III	Aristocort A® Cream 0.5%	fluticasone propionate
	Cutivate® Ointment, 0.05%	betamethasone dipropionate
	Diprosone® Cream, 0.05%	mometasone furoate
	Elocon® Ointment 0.1%	diflorasone diacetate
	Florone® Cream, 0.05%	...
	Maxiflor® Cream, 0.05%	
	Maxivate® Cream, 0.05%	
	Uticort gel®, 0.025%	

	Uticort g l®, 0.025% Valison ® Ointment, 0.1%	diflorasone diacetate b tamethason dipropionate betamethasone benzoate betamethasone valerate
IV	Aristocort® Ointment, 0.1% Cordran® Ointment, 0.05% Elocon® Cream, 0.1% Kenalog® Ointment, 0.1% Synalar® Ointment, 0.025% Topicort LP® Cream, 0.05%	triamcinolone acetonide flurandrenolide mometasone furoate triamcinolone acetonide fluocinolone acetonide desoximetasone
V	Aristocort® Cream, 0.1% Cordran® Cream, 0.05% Cutivate® Cream, 0.05% Dermatop® Emollient cream, 0.05% Diprosone® Lotion, 0.05% Kenalog® Cream, 0.1% Kenalog® Lotion, 0.1% Locoid® Cream, 0.1% Synalar® Cream, 0.025% Valisone® Cream, 0.1% Valisone® Lotion, 0.1%	triamcinolone acetonide flurandrenolide fluticasone propionate prednicarbate betamethasone dipropionate triamcinolone acetonide triamcinolone acetonide hydrocortisone butyrate fluocinolone

	Valisone Lotion, 0.1% Uticort® Cream 0.025% Westcort® Cream, 0.2% Westcort® Ointment, 0.2%	acetonide betamethasone valerat betamethasone valerate betamethasone benzoate hydrocortisone valerate hydrocortisone valerate
VI	Aclovate® Cream, 0.05% Aclovate® Ointment, 0.05% Synalar® Solution, 0.01% Tridesilon® Cream, 0.05%	alclometasone dipropionate alclometasone dipropionate fluocinolone acetonide desonide
VII: Low Potency	Numerous preparations exist	dexamethasone flumethalone hydrocortisone methylprednisolone prednisolone

Adapted from Stoughton.[1]

Group I is the superpotent category; potency descends with each group, to group VII, which is least potent (II, III, potent steroids; IV, V, midstrength steroids; VI, VII, mild steroids). There is no significant difference between agents *within* groups II through VII; the compounds are simply arranged alphabetically. *However*, within group I, Temovate® Cream or Ointment is more potent than Diprolene Cream or Ointment and Psoroon Ointment.

Intravaginal steroids have been used for lichen planus as a first line of treatment if vaginal involvement is present.

Cort-Dome vaginal suppositories are used in the following manner:

1/2 of a Cort-Dome suppository per vagina twice daily for 2 months, then daily for 2 months, then maintenance treatment at 1 to 3 times per week. However, many patients do not experience significant long-term response to intravaginal steroids. The vaginal vault tends to continue to scar. To keep the vault open and prevent adhesions it often will be necessary to use vaginal dilators. The dilator may be lubricated with a hydrocortisone cream.

Walsh et al. developed a method to occlude topical medication on the vagina following surgical release of labial adhesions. An aggressive approach to increase delivery of topical medications included a vaginal (and oral) prosthesis, use of the vaginal moisturizer (Replens) as a vehicle for corticosteroids, and iontophoresis. Rapid response was obtained, and a less-intensive dosing schedule has resulted in remission of over 1 year.

Open areas of limited size can be healed with intralesional triamcinolone acetonide injections at a concentration of 3 mg/ml.

At times a stronger steroid may be required. **Oral prednisone** at a dose of 40 mg – 60 mg each morning until healing has occurred. As the skin heals, topical corticosteroids may be added as the prednisone is tapered.